Prolonged Fractionation of Paced Right Atrial Electrograms in Patients With Atrial Flutter and Fibrillation

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OBJECTIVES This study investigated the extent of fractionation of paced right atrial electrograms in patients with and without paroxysmal atrial flutter (AFL) or atrial fibrillation (AF).

BACKGROUND Slow conduction through nonuniform anisotropic atrial muscles, represented by fractionated electrograms, may favor the generation of atrial tachyarrhythmias.

METHODS This study included 10 control patients (Group 1), 8 patients with documented paroxysmal AFL (Group 2) and 10 patients with documented paroxysmal AF (Group 3). Five electrode catheters were placed in the different sites of the right atrium and one catheter was positioned at the coronary sinus ostium. Atrial pacing from one site was done by a constant drive train with an extrastimulus inserted every fourth beat while recording at the other five sites was performed. The delay of each fractionated potential in the high-pass filtered atrial electrogram in response to extrastimulation was determined and used to construct conduction curves of delay versus the S1S2 interval.

RESULTS The mean increase in electrogram duration between a coupling interval of 350 ms and 10 ms above atrial refractoriness was significantly greater in Groups 2 and 3 compared with that in Group 1 (8.5 ± 2.5 vs. 11.0 ± 2.7 vs. 5.9 ± 2.3 ms, respectively, p < 0.001). The mean S1S2 interval at which delay increased suddenly was also longer in Groups 2 and 3 compared with Group 1 (326 ± 9 vs. 343 ± 12 vs. 307 ± 17 ms, respectively, p < 0.001).

CONCLUSIONS Increased delays in the individual potential of the fractionated atrial electrograms may be related to the development of AFL and AF. (J Am Coll Cardiol 2001;37:1651–7) © 2001 by the American College of Cardiology

Atrial fibrillation (AF) is the most common arrhythmia requiring treatment. On the basis of insights from human studies and animal models, AF is believed to result from multiple simultaneous reentrant wavelets sweeping across the surface of the atria, leading to an ever-changing pattern of electric excitation (1–4). It has been hypothesized that susceptibility to sustained atrial flutter (AFL) or AF can be quantitatively characterized by the magnitude of the tissue wavelength, defined as the product of refractory period and tissue conduction velocity, because the tissue wavelength determines the minimum size of a reentrant wavelet and the persistence of AF depends on the average total number of wavelets the tissue can support (1,5). If the conduction velocity is slowed, a given mass of atrial tissue can support a greater number of wavelets. Thus, increased intra- and interatrial conduction delays that can decrease the magnitude of the tissue wavelength have been demonstrated to be associated with clinical occurrence of paroxysmal AFL and AF (6–10). Furthermore, ventricular and atrial fractionated electrograms, which represent discontinuous propagation and slowed conduction, have been recorded in patients with healed myocardial infarction and those with paroxysmal AFL or AF, respectively (11–18). However, the extent to which the electrogram fractionation is related to the occurrence of AFL or AF has not been delineated. Therefore, in the present study, we tested the hypothesis that patients with AFL or AF have diseased substrates that result in greater fractionation of the paced right atrial electrograms compared with the control patients.

METHODS Patient characteristics. The study population consisted of 28 patients, including 10 with paroxysmal supraventricular tachycardia (n = 9) or nonsustained ventricular tachycardia (n = 1) but without any clinically documented AFL or AF (Group 1), eight with clinically documented paroxysmal AFL (Group 2) and 10 with clinically documented paroxysmal AF (Group 3) who were referred to receive electrophysiologic study and/or radiofrequency catheter ablation. Group 1 had six men and four women; their mean age was 58 ± 14 years (range 31 to 75 years); four had hypertension and one had coronary artery disease. Group 2 had four men and four women; their mean age was 61 ± 15 years (range 42 to 81 years); three had hypertension and one had coronary artery disease. Group 3 had nine men and one woman; their mean age was 64 ± 16 years (range 27 to 86 years); two had hypertension and three had coronary artery disease.
Catheter positions. A signed consent form was obtained from all patients. As described previously, all antiarrhythmic drugs were discontinued for at least five half-lives before the study (9). A 7F deflectable decapolar catheter with 2 mm interelectrode distance and 5 mm space between each electrode pair was inserted into the coronary sinus via the internal jugular vein; position of the proximal electrode pair at the ostium of the coronary sinus was confirmed with contrast injection. Five quadripolar catheters with 2 mm interelectrode distance and 5 mm space between two electrode pairs were introduced from the right and left femoral veins and placed at the high anterior wall, low anterior wall, high posterior wall, low posterior wall and septal wall close to the foramen ovale in the right atrium for recording and stimulation (Fig. 1A). Stability of the electrode catheters was maintained by fluoroscopic monitoring.

Study protocol. A programmed digital stimulator (DTU-210 or 215, Bloom Associate Ltd., Reading, Pennsylvania) was used to deliver electrical impulses of 2.0 ms at twice the diastolic threshold. Only the distal electrode pairs of the five atrial catheters and the proximal electrode pair of the coronary sinus catheter were used for electrical stimulation and electrogram recording. A pacing sequence was delivered from one electrode pair and bipolar electrograms were recorded at the other five electrode pairs. This sequence was repeated five times by pacing from the other five electrode pairs. The pacing sequence consisted of a 500-ms drive train with an extrastimulus applied every fourth beat followed by immediate resumption of the drive train. The extrastimulus coupling interval was reduced successively by 10 ms on each occasion from 450 ms until the atrial effective refractory period was reached. If AFL or AF was induced during the study, the pacing sequence was repeated at least 10 min after spontaneous or electrical conversion to sinus rhythm.

Data analysis. Intracardiac bipolar electrograms were recorded from the nonpaced electrodes over a frequency range of 30 to 500 Hz and were digitized at 1 KHz with 12-bit accuracy. All unsatisfactory electrograms that showed fusion with ventricular beats or failure to capture were rejected from the analysis. Data acquisition and analysis were performed by LabView software (National Instruments Co., Austin, Texas). The first phase of the analysis was performed to distinguish physiologically significant potentials from those related to background noise (19,20). The electrograms in response to an extrastimulus were processed with a digital, zero-phase high-pass filter with a −3 dB point of 150 Hz. This technique emphasizes small, sharply defined potentials in the electrogram related to local depolarizations and rejects slowly moving components, such as the intracardiac T-wave of the last drive cycle, while preserving the relative timings of each potential. The amplitudes of the samples between 150 and 200 ms after the extrastimulus were measured to determine the signal noise. The detection threshold was set at twice the maximum noise amplitude. The length of the electrogram was determined by fitting separate interpolating cubic splines to both the maxima and the minima in the electrogram as a function of time. The earliest and latest points at which these interpolating functions decreased to below the detection threshold were taken as the initial and final limits of the electrogram.
Table 1. Comparison of Anterior and Posterior Right Atrial Electrogram Fractionation

<table>
<thead>
<tr>
<th>S1S2 with increased delay (ms)*</th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 8)</th>
<th>Group 3 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>303.22</td>
<td>313.90</td>
<td>326.63</td>
</tr>
<tr>
<td>SD</td>
<td>21.84</td>
<td>6.75</td>
<td>19.94</td>
</tr>
<tr>
<td>Increase in electrogram duration (ms)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.44</td>
<td>8.04</td>
<td>9.87</td>
</tr>
<tr>
<td>SD</td>
<td>1.40</td>
<td>3.96</td>
<td>1.13</td>
</tr>
</tbody>
</table>

*A vs. P in all three groups, p < 0.001. Group 1 vs. 3, p = 0.003; group 1 vs. 2 and group 2 vs. 3, p > 0.05; †A vs. P in all three groups, p = 0.001. Group 1 vs. 3, p = 0.003; group 1 vs. 2 and group 2 vs. 3, p > 0.05.

A = anterior right atrium; P = posterior right atrium; SD = standard deviation.

All potentials within these limits that were greater than twice the detection threshold were extracted, and their delays after the pacing spike were determined to construct a conduction curve of the delay of individual potentials at each extrastimulus coupling interval (Fig. 1, B and C). The number of potentials in each electrogram was also calculated.

The second stage of the analysis reduces the conduction curves to simple parameters of statistical analysis (19,20). The envelopes of the curves were defined by identifying the first and last components of the electrogram at each S1S2 coupling interval. These envelopes were then smoothed by curve fitting to extract two parameters that were designed to reflect the arrhythmogenic potential of the tissue (Fig. 1C). Several curve-fitting techniques available in the LabView software, including general polynomial fit and general LS linear fit, were evaluated using conduction curves from six Group 1 and Group 2 patients. The final decision was made on the basis of the smoothness of the fitted curve and the dispersion of patients in the same group in the scattergram. It was found that the general polynomial fit using singular value decomposition (SVD) gave the tightest distribution (the smallest standard deviation) and smooth fitted curve. Thus, general polynomial fit using SVD was used in the following analysis. The first parameter was the difference between the electrogram duration at an S1S2 interval of 350 ms and at 10 ms greater than atrial effective refractory period. This parameter reflected the ability of the tissue to create dispersion of activation and hence an arrhythmogenic substrate. The second parameter was the S1S2 coupling interval at which delays start to increase to >0.75 ms/20 ms decrease in S1S2 interval (which is the lowest stable threshold in the presence of signal noise). This reflected the ease with which a substrate, activation delay, can be exposed with a stimulus and so may relate the vulnerability of the tissue to arrhythmogenic stimuli. The maximum number of potentials in the electrograms recorded at any S1S2 interval was also measured. The mean increase in the electrogram duration, the mean S1S2 interval at which delay increased and the mean maximal number of potentials in the electrograms recorded at any S1S2 interval were obtained from the average of all 30 sets of conduction curves and was used as an independent observation to describe the intra-atrial conduction in a particular patient (Fig. 1D).

**Statistical analysis.** Quantitative values are expressed as mean ± SD. The two-way repeated-measures analysis of variance test with Bonferroni method for multiple comparison was used to compare anterior and posterior right atrial electrogram fractionation in the three groups (Table 1). The Kruskal-Wallis test was used for comparison of the mean increase in the electrogram duration, the mean S1S2 interval at which delay increased and the mean maximal number of potentials in the electrograms recorded at any S1S2 interval among the three groups. Discriminant analysis, including Fisher linear discriminant functions and jackknife method, was performed to separate the three groups in the scattergram on the basis of parameters of the mean increase in the electrogram duration and mean S1S2 interval at which delay increased (21,22). A value of p < 0.05 was considered statistically significant.

**RESULTS**

Two sets of electrograms obtained from the high posterior right atrium while the high anterior wall was paced are shown in Figure 2. The left-hand set was obtained from a control patient and the right-hand set was obtained from a patient with AF. The electrograms in each pair were recorded in response to the same stimulus-coupling interval during the pacing protocol. The electrograms from the patient with AF demonstrate that with increasing stimulus prematurity, there is increasing fragmentation in the electrogram and increasing latency of its individual potentials. Figure 3A shows a conduction curve from a control patient. There is a slight fluctuation in the delay with premature stimulation until it increases rapidly at S1S2 intervals below 220 ms. Figure 3B shows a conduction curve from a patient with AFL. There is a rapid increase in delay and a gradual increase in electrogram duration at S1S2 intervals below 260 ms. Figure 3C shows a conduction curve from a patient with AF. There is a gradual increase in delay and electrogram duration at S1S2 intervals below 310 ms.

The mean increase in the electrogram duration was significantly greater in patients with AFL and AF compared with that in control patients (8.5 ± 2.5 vs. 11.0 ± 2.7 vs.
greater in the smooth posterior wall than in the trabeculated anterior wall in all three groups.

**DISCUSSION**

**Major findings.** The present study demonstrated that in response to an extrastimulus, patients with AFL or AF develop fractionated electrograms more easily, and each fractionated potential has greater delay than in control patients. These findings suggested that increased intra-atrial conduction delay and dispersion may create a reentrant substrate for clinical occurrence of AFL and AF.

**Intra-atrial conduction delay.** The correlation between the presence of intra-atrial conduction abnormalities and the induction of AFL and AF has been well established. Patients with histories of paroxysmal AFL or AF have been shown to exhibit significant intra-atrial conduction delays during early premature impulses delivered at the right atrium (6–8). Furthermore, Papageorgiou et al. (10) have demonstrated that the existence of site-dependent intra-atrial conduction delays is a common property of the human atrial myocardium; during high right atrial stimulation, patients with AF inducibility exhibited significant prolongation of conduction to the posterior triangle of Koch and marked broadening of the posterior triangle of Koch electrogram compared with coronary sinus stimulation. In the present study, we addressed the ease with which intra-atrial conduction delays can be exposed in patients with AFL and AF on the basis of the finding that patients with AFL and AF exhibited a longer S1S2 interval. At this interval, delay of potential within the electrograms increased markedly compared with control patients. These results further address the important role of decreased conduction velocity in the development of atrial tachyarrhythmias. Saumarez et al. (20) also reported that whereas conduction delay discriminates between primary ventricular fibrillation patients and control patients, the increase in the number of fractionated potentials does not distinguish between them. A prolonged and fractionated electrogram may be generated by various mechanisms: 1) spatial dispersion in refractory period (23); 2) tissue anisotropy resulting in a zigzag course of the propagating depolarization wave front on a microscopic level owing to scarce side-to-side electrical coupling (24); and 3) the presence of insulating collagenous septa between atrial muscle bundles (24).

In the present study, using two discriminant lines in the scattergram of change in electrogram duration versus onset of increase in potential delay, the three groups could be significantly separated with an accuracy of 71.4%. None of the patients with AF was misclassified. However, one of the control patients was placed in the AFL group; one patient with AFL was in the control group and the other in the AF group. This finding could be explained by the evidence that patients with AF have atria with more generalized disease, but the remaining two groups have atria with limited disease, therefore patients in Groups 1 and 2 are misclassified because the
arrangement of electrode catheters may not be ideal for them. Although most of the evidence suggests that AF originates in the left atrium (25,26), from the results of this study we would conclude that the right atrium is diseased in all patients with AF irrespective of where AF actually starts.

**Different electrophysiology between the anterior and posterior right atria.** Hashiba et al. (27) have found a significantly greater number of abnormally prolonged and fractionated endocardial electrograms distributed in the high posterolateral right atrium in patients with sick sinus syndrome irrespective of the presence or absence of paroxysmal AF. Using animal models of AF, Li et al. (23) reported that disorganized epicardial atrial electrograms were observed mainly at the right posterolateral atrium, which had the longest atrial effective refractory period. Jais et al. (18) also found regional disparities of endocardial atrial
activation during paroxysmal AF; in the right atrium, the septal and the posterior areas were significantly more disorganized than the lateral and anterior regions.

In the present study, the mean S1S2 interval at which delay increased was significantly longer, and the mean increase in the electrogram duration were significantly greater at the posterior wall compared with the anterior wall in patients with or without AFL and AF. This finding suggested a delayed and nonuniform anisotropic conduction through a more diseased posterior right atrial muscle, supported by the histologic evidence that endocardial hypertrophy, a process of proliferation of smooth muscle cells and collagen fibers beneath the endocardial lining, is more marked in the posterior wall of the atria at all times (28).

Study limitations. Although the right atrium exhibits increased intra-atrial conduction delay in response to premature stimulation in patients with AFL or AF, the quantitative relation between left and right atrial involvement is unknown. This issue needs investigation through the use of more recording electrodes within the left and right atria and pacing from more sites to determine an optimum electrode arrangement. Because bipolar electrograms were measured and the signals were high-pass filtered, small fractionated features of the electrogram were emphasized and assumed to represent activation of fibers close to the electrode. However, bipolar electrodes are directional, and this may bias the detection of different activation processes. Another concern is that induction of AFL or AF during the pacing sequence may produce a temporal change of conduction velocity and bias the measurement. However, we always waited at least 10 min after termination of arrhythmia to repeat the pacing sequence.

Clinical implications. During electrophysiologic evaluation of symptomatic patients with suspicious AF but without documentation on ECG, it is often difficult to establish a level of programmed stimulation that unmasks the pathologic substrate of AF rather than creating a general response that is of no clinical significance. The test described in this study may reveal the presence of a substrate of AFL or AF in a more specific way than programmed stimulation.

Conclusions. The present study demonstrated that individual potential within fractionated atrial electrograms has increased delays in patients with paroxysmal AFL or AF when compared with control patients. This finding suggests that slow and inhomogeneous intra-atrial conduction attributable to the diseased atrium may be related to the development of atrial tachyarrhythmias.

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REFERENCES